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Guidelines for Clinical Studies with Compression Devices in Patients with Venous Disorders of the Lower Limb

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Objectives. *The scientific quality of published clinical trials is generally poor in studies where compression devices have been assessed in the management of venous disease. The authors' aim was to establish a set of guidelines which could be used in the design of future clinical trials of compression treatments for venous diseases.*
Design. *Consensus conference leading to a consensus statement.*
Methods. *The authors form a expert consensus group known as the International Compression Club (ICC). This group obtained published medical literature in the field of compression treatment in venous disease by searching medical literature databases. The literature was studied by the group which attended a consensus meeting. A draft document was circulated to ICC members and revised until agreement between contributors was reached.*
Results. *The authors have prepared a set of guidelines which should be given consideration when conducting studies to assess the efficacy of compression in venous disease.*
Conclusions. *The form of compression therapy including the comparators used in the clinical study must be clearly characterised. In future studies the characteristics of the material provided by the manufacturer should be described including in vivo data on pressure and stiffness of the final compression system. The pressure exerted on the distal lower leg should be stated in mmHg and the method of pressure determination must be quoted.*

Keywords: Compression devices; Clinical studies; Guidelines; Venous disorders; International compression club.

Introduction

The level of clinical trials in which compression devices are used to treated venous disease is frequently poor,[1,2] with lack of standardisation in methodology and measurement. It is desirable to develop a set of guidelines for clinical trials with compression devices In order to ensure a consistent approach in design and reporting of data. Currently no guidelines have been published either on a national or an international level.

Methods

These guidelines were prepared by a group of distinguished experts each of whom has published scientific work in the field of venous disease (Table 1). This group refers to its members as the 'International Compression Club (ICC). Published papers relevant to these guidelines are identified from searching the medical literature databases Medline and Embase, and on the UIP-consensus on evidence-based compression-therapy.[2] The meeting of the ICC at which the first draft of the guidelines was discussed took place in Cologne the 17th September 2005. The results of this discussion were included in a further draft which was then sent by e-mail to the experts of the group for further comment. Further versions of the document were circulated to the group until

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Table 1. Members of the International Committee who agreed with the consensus statement

M. Abel, Germany	CH. Moffat, UK
I. Achhammer, France	F. Pannier, Germany
A. Andriessen, Netherlands	H. Partsch, Austria
F. Becker, France	K. Peters, UK
D. Bender, USA	E. Rabe, Germany
J-P. Benigni, France	A.A. Ramelet, Switzerland
J-C. Bouvier, France	H. Schepers, Switzerland
A. Cornu-Thenard, France	J. Schuren, The Netherlands
C. Feenstra, Netherlands	M. Spengler, Germany
J. Greve, Germany	U. Schettler, Germany
J. Hutchinson, UK	K. Tucker, Germany
K. Ißberner, Germany	J. F. Uhl, France
M. Jünger, Germany	W. Vanscheidt, Germany
D. Kolbach, Netherlands	P. Zöllner, Germany

Table 2. Requirements for a study-protocol

- Background of the study (literature review and risk management assessment),
- primary (and if applicable secondary) objective(s),
- the design (controlled, open, randomized, multi-centre etc.),
- the population (detailed description of the disease, inclusion and exclusion criteria),
- duration of the study and/or treatment,
- number of visits and interventions at the different visits (study flow chart),
- detailed description of the treatment and comparator or control,
- primary and secondary outcome parameters,
- statistical planning of evaluation and sample size calculation.
- additional documents or approvals include patient information and consent forms, ethics committee statement, case report forms, patient insurance,
- the Declaration of Helsinki, and a list of references

agreement of all members was obtained. The resulting text appears below.

General, legal and formal aspects

Studies must be planned, conducted and evaluated according to current directives and guidelines, examples of which are given at the end of this chapter.[3,4,5,6,7] It is a legal requirement to follow local or national laws concerning the conduct of clinical trials, and this takes precedence over international guidelines. As differing directives and guidelines may apply in different countries, investigators must ensure that the relevant national instructions are taken into account. It is recognised that directives and guidelines change, so it is important to ensure that the most recent version of these documents is identified and used.

In order to conduct a clinical trial of the efficacy and safety of a treatment or method with uncertified medical devices, approved medical devices or handling instructions used in off-label indications or with additional unusual burdens for the patient, a study protocol with all additional necessary documents or approvals must be prepared. The items that must be clearly described are listed in Table 2.

Registration with or approval by the relevant national authorities may be necessary depending on the national or local law.

The results of the study should be summarised in a clinical, biometric report containing critical comments on the study concept, the study methodology and interpretation of the results, and take into account the clinical and scientific knowledge available. The report should draw conclusions for the medical profession, the medical device manufacturer and, where appropriate, the health authorities and any other bodies. This comprehensive report constitutes part of the clinical trial and is necessary regardless of whether or not the study is to be published. The conduct of clinical studies with certified medical devices used in their certified indications or 'instructions for use' are governed by minor regulatory requirements − also dependent on the current national or local law.

Examples of directives and guideline and internet URLs:

- ICH (International Conference of Harmonisation) e.g. Topic E 6: Guideline for Good Clinical Practice in the European Community. (www.ich.org)
- DIN ISO EN 14155-1/-2: 'Clinical investigation of medical devices for human subjects − Part 1: General requirements'. Part 2: Clinical investigation plans' (edited by Beuth Verlag, www.beuth.de)
- MEDDEV 2,12−2 May 2004 'Guidelines on post market clinical follow-up'. (http://europa.eu.int/comm/enterprise/medical_devices/meddev/)
- MEDDEV 2.7.1. Clinical investigation, clinical evaluation, Guide for manufacturers and notified bodies

General comments on the classification of chronic venous disorders

The CEAP classification system for chronic venous disorders takes into account clinical, etiological, anatomical and pathophysiological factors. Its informative value has been validated. We therefore recommend that patients with chronic venous diseases be classified according to their CEAP classification for future studies. In addition, the CEAP classification system offers a limited assessment of changes in the clinical scoring system.[8] The use of the *Basic CEAP classification* is mandatory.[8]

For studies that require greater patient differentiation the *Scientific CEAP classification* is recommended.[8] However, since CEAP is mainly a descriptive

classification, additional instruments should be used to assess the outcome after therapy (e.g. Venous severity scoring VSS).[9]

In studies on patients with acute venous diseases the classification must include exact localisation, extent and duration of the changes.

Requirements

1 Principal requirements

The form of compression therapy including the comparator(s) used in the clinical study must be characterized.

Medical compression garments
The following data should be given:

- type and size of the compression garment (calf, thigh)
- the kind of material, flat or round knitted
- the pressure range at ankle level (mm Hg, measuring method), pressure according to manufacturer's labelling
- the pressure gradient
- Ready to wear or made to measure

The following data should be encouraged:

- Slope/stiffness of the material
- *In vivo* pressure values

The compression garment used must be marked (e.g. with a code) to ensure that the same garment is used during the study.

Compression bandages
The following data should be given:

- Material, number and type of components
- Size (length with and without stretch, width) of the bandage (if measured with stretch the percentage of stretch needs to be given)
- Length of the bandage system (calf, thigh)
- Technique of application (spiral, figure-of eight, overlap)

The following data should be encouraged:

- Stiffness of the final bandage (system)
- *In vivo* pressure values

The size of the ankle should be recorded in all trials. This ensures that the correct choice of bandages is made for all patients. While most ankle sizes range from 20 to 25 cm there is a proportion with very small and large limbs.

Pumps and other mechanical devices

- Number and type of pressure chambers
- Pressure distribution
- Pressure applied
- Pumping cycles
  - Inflation and deflation characteristics
  - Duration
  - Number

In comparative trials the above-mentioned characteristics should be declared for all compression devices tested or used.

2 Further requirements

The following points should be considered depending on the details of the study:

Material
The declaration of fibre content, extensibility in longitudinal and transverse direction and of stiffness (hysteresis-curve) are desirable (see above).

The influence exerted by the compression product on resting and working pressures depends upon the extensibility of compression material. The elastic properties of a compression bandage or system are affected by the number of layers in the system, whereby the greater the number of layers, the greater the effect. Details on the number and nature of layers must be provided.

In future studies the characteristics of the material provided by the manufacturer should be declared including the *in vivo* data on pressure and on stiffness of the final compression system on the individual leg.[10]

It has to be declared whether bandages have been washed or not.

Person applying the compression device
Compression trials are very user dependant. Every attempt should be made to limit the number of people applying the bandages within a trial as considerable variation occurs between experienced bandagers. All personnel involved in applying bandages (patient, relatives, medical staff) should have a formal standardized training which includes pressure measurements of their technique.

Duration of compression and concordance
The time of compression per day and the total wear time must be noted and patients' concordance must be documented.

Concordance where possible should be recorded by the patient and assessed by a blinded assessor to avoid the temptation of labelling "deviant" patients.

Previous compression therapy
What kind and for how long.

Durability and costs
Durability, reusability and costs of the material should be described where applicable.

Cost-effectiveness
Cost-effectiveness evaluation is desirable in clinical studies depending on the size and nature of the study. There is a wide range of possible analyses including cost minimisation, cost reduction, cost-benefit relation etc. Clinical trials should aim to measure cost effectiveness which allows both clinical and cost outcomes to be considered together.

Physical activity
Physical activity and walking ability of the patient (ADL = Activities of daily living) should be described. The daily walking distance or activity may be measured using a pedometer.

Validated tools for measuring activities of daily living are recommended. Independent risk factors for ulcer healing have been identified, like general mobility status (chair/bedbound, walking outside unaided, walking inside aided and walking freely) and ankle function (full movement, reduced ankle function, fixed ankle joint).

Quality of life
Patient reported outcome (PRO) and Quality of life (QoL). Validated, disease-specific and generic Quality of life questionnaires should be used.[11,12,13,14]

Pressure
The pressure exerted on the distal lower leg should be given in mmHg and the method of pressure determination must be quoted. Report of in vivo pressure using a pressure sensor specific to a manufacturer is not recommended. Compression classes vary considerably between different countries (Table 3).

In order to find a clear and internationally acceptable language we propose to replace compression classes by pressure ranges at the ankle region, declaring the in vitro-method of measurement: e. g. 10–20 mmHg, 20–30 mmHg, 30–40 mmHg, >40 mmHg.

The pressure values given by the manufacturers of medical compression hosiery are measured by different methods (e.g. ITF, HOSY, HATRA). For future trials the additional measurement of *in vivo* pressure is encouraged.

Several instruments are available for measuring the *in vivo* -pressure exerted by compression garments on patients' limbs.[15,16] Recommendations as to how and where the pressure should be measured have been proposed by the ICC.[17] Several important points have to be considered (Table 4).

It is recommended that any pressure sensor that is considered for use should satisfy, or come close to, the following key specifications:[17]

- The sensor should be thin and flexible. Based on theoretical model calculations that are mainly valid for flat areas a maximal sensor thickness of 0.5 mm is suggested.
- The sensitive area of the sensor should be adjustable and optimized for different applications (leg, hand, toe) and different measuring regimes: e. g. small areas for mapping of a circumferential pressure pattern, large sensor areas (over 5 cm^2) for measuring the integral pressure of a larger area taking advantage of the fact that the local pressure distribution will be averaged over changing curvatures of the leg segment.
- The sensor should be able to be left in contact with the leg for extended periods of time without skin irritation and should keep its accuracy.

Table 3. Compression classes of compression hosiery used in several countries. (Values in mmHg, 1 mmHg = 1,333 hPa)

Compression Class	USA	UK (BS 6612)	France	Germany
I	15–20 (moderate)	14–17 (light)	10–15	18–21 (light)
II	20–30 (firm)	18–24 (medium)	15–20	23–32 (medium)
III	30–40 (extra firm)	25–35 (strong)	20–36	34–46 (strong)
IV	40+		>36	>49 (very strong)

The values indicate the compression exerted by the hosiery at a hypothetical cylindrical ankle.

Table 4. Measurement of sub-bandage pressure is influenced by several factors

Pressure Sensors	Site of sensor Application	Method of Application	Position of limb
Small diameter sensors tend to report peak pressures	Sensor placed over soft tissue or flat parts of the leg may show lower pressures than when placed on a hard area or on curved parts	Factors affecting pressure	Pressures are higher when standing and significantly altered during walking
Inflexible sensors-artificially high readings due to lack of conformability		Figures of eight or Spiral Number of layers Degree of overlap	

- Pressure measurement systems that allow continuous pressure measurement during active or passive patient movement (e.g. muscle pump test or tilt test) are preferred.
- Easy sensor calibration conducted ideally before each measurement.
- Multiple sensors allowing concurrent measurement of pressures under the device at several anatomical sites may be preferred over single sensors.

Methods of Measurement

Parameters and methods

Many parameters and methods are applicable for measuring a variety of compression effects (Table 5). This does not mean that all methods should be used together in future trials. Methods should be selected according to the specific objective of the study.

For any vein diameter or any haemodynamic parameter the position must be specified (supine position, sitting position, standing position on both feet or on contralateral foot).

Definition of the level of arterial disease, an ABPI of 0.8 or above can be accepted.

In ulcer trials risk factors that affect healing rates should be documented, e. g. Body Mass Index (BMI). At least ulcer size and ulcer duration, which are the two most important predictive factors.

Examples for outcome parameters in future compression studies

The outcome parameters used and presented should be selected according to the different stages of chronic venous diseases included in trials (Table 6). All methods used for clinical studies must be validated. In all CEAP stages, quality of life, standardized evaluation of patients' satisfaction, venous severity scoring, changes in CEAP-classification, and VAS for subjective complaints should be used. In all stages compliance with compression must be documented. For standardized photodocumentation, assessment by blinded observers is preferred. Long term assessment is preferred in all stages although it is recognised that this may not always be feasible. (Table 6)

Table 5. Parameters and methods

Endpoint	Methodology
Vein diameter	ultrasound, phlebography
Venous compliance	pressure/volume relationship using simultaneous measurements of venous pressure and of volume
Lympatic drainage	lymphoscintigraphy, fluorescence microlymphoangiography, indirect x-ray lymphography, intralymphatic pressure measurement
Leg volume	water displacement volumetry, ultrasound, optoelectonic instruments, computerized digital photography, other validated methods
Microcirculation	laser Doppler fluxmetry (to assess the veno-arteriolar reflex and vasomotor activity), transcutaneous oxygen tension, capillaroscopy, skin biopsy
Treatment effects, e.g. sclerotherapy, laser or venous surgery	efficacy parameters, effects on the frequency of side effects like phlebitis, pigmentation, bruising, pain etc
Recanalisation of a vein	duplex, measurement of outflow fraction by strain gauge or air plethysmography (APG), quantitative assessment of refluxes by measuring venous filling index (ml(sec) using APG
Lipodermatosclerotic skin changes	skin thickness with high frequency ultrasound (e.g. 20 MHz), CT, NMR, by the durometer, tissue compliance monitor[18,19]
Ulcer healing	incidence of complete healing, area-planimetry, area in $cm^2 \times \pi/4$ (ellipse), Gillman method healing rate per unit time with correction for ulcer size $(A_b - A_a)/(P_a + P_b)/2)$ (b−a) [A: area of ulcer, P: perimeter, a: start and b: end of the observation], time to complete healing, life table analysis should include all patients, including those lost to follow up and treatment failures[20]
Clinical parameters	symptoms on analogue scale including pain, CEAP, classification and VSS, QoL

Table 6. Examples for specific outcome parameters in different stages of VD

Disease	C of CEAP	Outcome Parameters
Subjective symptoms without clinical signs	C0, S	occurrence rate and severity of symptoms
Teleangiectases, reticular veins, symptomatic	C1, S	visual analogue scale (VAS) for the subjective complaints
Small varicose veins after sclerotherapy or laser treatment	C1	clinical improvement type and frequency of complications
Large varicose veins, asymptomatic	C2, A	frequency of clinical progression and complications occurrence of subjective complaints
Large varicose veins, symptomatic	C2, S	VAS for subjective complaints frequency of clinical progression and complications
Large varicose veins in pregnancy	C2, A, S	frequency of clinical course (progression/regression) and complication occurrence of subjective complaints, venous diameter and reflux
Large varicose veins after surgery, sclerotherapy, endovenous laser or radiofrequency treatment	C2–C6	clinical improvement frequency of complications occlusion rate, reflux recurrence rate
Venous oedema (including postthrombotic oedema and oedema in angiodysplasias)	C3	measurement of volume changes by: standardized circumference measurements volumetry (water displacement, optoelectronic, digital camera+computer)
Skin changes (eczema, pigmentation)	C4a	eczema score thermography, colorimetry
Skin changes (lipodermatosclerosis, white atrophy)	C4b	rate of progression and improvement durometer, ultrasound B-scan (thickness and texture), CT, NMR, thermography
Healed ulcer	C5	rate of ulcer recurrence (at the site of ulcer, a new area of ulceration on the same limb and contra lateral limb)
Active ulcer	C6	rate of ulcer-healing, healing-time. (Detailed wound documentation with description of different wound parameters over the treatment period and follow-up phase.)
Prevention of venous thromboembolism		DVT-rate pulmonary embolism-rate superficial phlebitis-rate
Superficial phlebitis		improvement of symptoms (e.g. pain) and signs (inflammation) assessment of thrombus extension in superficial and/or deep veins, occurrence of pulmonary emboli
Deep vein thrombosis (DVT), early onset		change of thrombus size symptoms (pain) oedema formation occurrence of pulmonary emboli (repeated V/Q-scans) DVT-recurrence (rate), death occurrence of post-thrombotic syndrome (rate, time)
Prevention of post-thrombotic syndrome (PTS) after DVT		DVT-recurrence (rate), death subjective symptoms (pain, heaviness) oedema formation (leg volume) skin changes reflux/occlusion (rate)

Establishing a reliable diagnosis of chronic venous disorders and acute venous diseases

It must be reliably determined that the clinical findings in each study subject are the result of a disturbance of venous haemodynamics. A clinical examination is not sufficient to do this.

The clinical picture as well as the pathological changes need to be specified using imaging and functional methods:

Imaging methods include duplex sonography, phlebography or MRI which can be used to localise a venous disorder in the sub- and extra-fascial venous system.

Functional methods include duplex and Doppler sonography to demonstrate reflux in the superficial and/or deep veins. Phlebodynamometry (measurement of intravenous pressure) is currently to be regarded as the reference procedure to record venous pumping action. Alternative methods include various forms of plethysmography such as the strain gauge method, foot volumetry and photoplethysmographic methods.

Acute venous diseases must be documented and classified by imaging methods (e.g. duplex, phlebography).

Study Criteria

1 Inclusion criteria

- Signed informed consent declaration/data protection declaration
- Exact diagnosis based on the CEAP classification

2 Precautions

The following points which may be exclusion criteria should be carefully considered

- Diseases/symptoms that imitate the symptomatology of venous disease (e.g. lymphoedema, lipoedema)
- Heart failure
- Severe renal and hepatic failure
- Competing/interfering, concomitant systemic and local drug treatments (no newly started medication with a vascular or cardiovascular effect should be taken/administered during the treatment)
- Known allergies to the compression material

- Patients who have already taken part in another study with the same objective up to 3 months before entering this study
- Patients who have already taken part in the study
- Asymptomatic and symptomatic peripheral occlusive arterial disease, malleolar artery pressure values with a reduced ankle/arm index (<0.8) (if not indicated in the designed study population, e.g. mixed leg ulcers)
- Limited mobility of the study leg (e.g. paralysis) if not part of the study design

3 Concomitant treatment

Continued treatment of other diseases is allowable depending on the test parameters chosen, and with the proviso that the treatment will not interfere with the trial outcome. Any concomitant medication must be recorded.

4 Withdrawal criteria

- Deterioration in the clinical picture of venous disorders (e.g. progression to a higher stage of CVI) if not indicated in the designed study population
- Lack of concordance by the patient
- Withdrawal of patients consent (reasons for withdrawal of patient consent should be documented)
- Change in measures and events that affect the target criteria *Example:* Initiation, change or discontinuation of hormone therapy, diuretic treatment
- Intercurrent infections of the lower extremity

Perspective

The present recommendations for testing the therapeutic efficacy of compression treatments in patients with venous disorders are designed to help to determine the significance of the various treatment modalities more accurately and consistently by means of qualified clinical studies.

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